

## Curriculum vitae

**Name:** Yasumichi Hitoshi, MD. Ph.D.  
**Born:** November 21, 1961. Kumamoto, Japan  
**Citizenship:** Japan

**Present Position:** Director, Oncology  
**Present address:** Rigel pharmaceutical Inc.,  
1180 Veterans Boulevard,  
South San Francisco  
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### Professional experience:

2003.7-present      Director, Oncology  
Department of Cell Biology  
Rigel pharmaceutical Inc.  
Research and Development: Identification and validation of drug targets for cancer therapy, and development of anti-cancer drugs.

2002.7-2003.7      Associate director, Project leader  
Department of Cell Biology,  
Rigel pharmaceutical Inc.  
Research: Validation of drug targets for inhibition of tumor cell growth or sensitization of tumor cells to the effects of chemotherapeutic agents via cell cycle regulation.

2002.1-2002.7      Group leader, Project leader  
Department of Cell Biology,  
Rigel pharmaceutical Inc.  
Research: Validation of drug targets for inhibition of tumor cell growth or sensitization of

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tumor cells to the effects of chemotherapeutic agents via cell cycle regulation.

- 1998.12-2001.12    Senior scientist, Project leader  
Department of Cell Biology,  
Rigel pharmaceutical Inc.  
Research: Identification of proteins and peptides that play an important role  
in cell cycle regulation of specific tumor cells using retroviral  
functional screens.
- 1998.2-1998.12    Senior scientist  
Department of Cell Biology,  
Rigel pharmaceutical Inc.  
Research: Characterization of a membrane receptor, Toso, which inhibit  
TNF receptor family-induced apoptosis.
- 1995.3-1998.2    Postdoctoral Fellow  
Department of Molecular Pharmacology, Stanford University.  
Research: Analysis of signaling pathway using high titer retrovirus.  
Scientific Advisor: Assistant Professor Garry P. Nolan
- 1992.1-1995.3    Postgraduate Research Associate  
Department of Immunology,  
The Institute of Medical Science,  
The University of Tokyo.  
Scientific Advisor: Professor Kiyoshi Takatsu  
Research: Cellular mechanism of development of a retrovirus-  
induced immunodeficiency syndrome (MAIDS)
- 1991.4-1991.12    Postgraduate Research Associate  
Department of Biology,  
The Institute for Medical Immunology,  
Kumamoto University Medical School.  
Scientific Advisor: Professor Kiyoshi Takatsu  
Research: Signal transduction through IL-5 receptor and  
involvement of Xid defect in the receptor system.

**Education:****Medical School**

1981-1987      Kumamoto University Medical School

**Graduate School**

1987-1991      Department of Biology,  
The Institute for Medical Science,  
Kumamoto University Medical School  
Research: Immunology  
Scientific Advisor: Professor Kiyoshi Takatsu  
Thesis Dissertation: Role of interleukin 5 and its receptor in the immune system.

**Membership of learned societies:**

American Association for Cancer Research  
The American society for Cell Biology

**Honors and Fellowships**

Special Fellow of The Japanese Ministry of Education, Culture and Science,  
April 1990-March 1991.  
The Uehara Memorial Foundation Fellowship, April 1995-March 1996.

## Publications

1. Mita, S., Harada, N., Naomi, S., **Hitoshi, Y.**, Sakamoto, K., Akagi, M., Tominaga, A. & Takatsu, K., (1988). Receptors for T cell-replacing factor / Interleukin 5 Specificity, quantitation, and its implication. *J. Exp. Med.*, 168, 863 - 878.
2. Jankovic, D.L., Abehsira-Amar, O., Korner, M., Roth, C., **Hitoshi, Y.**, Takatsu, K. & Theze, J., (1988). IL-4, but not IL-5, can act synergistically with B cell activating factor (BCAF) to induce proliferation of resting B cells. *Cell. Immunol.*, 117, 165 - 176.
3. **Hitoshi, Y.**, Mita, S., Tominaga, A., Kikuchi, Y., Sonoda, E., Takatsu, K. & Watanabe, Y., (1989). Interferon-gamma inhibits the proliferation but not the differentiation of murine B cells in response to IL-5. *Int. Immunol.*, 1, 185 - 190.
4. Tominaga, A., Mita, S., Kikuchi, Y., **Hitoshi, Y.**, Takatsu, K., Nishikawa, S.-I. & Ogawa, M., (1989). Establishment of IL-5-dependent early B cell lines by long-term bone marrow cultures. *Growth Factors*, 1, 135 - 146.
5. Matsumoto, R., Matsumoto, M., Mita, S., **Hitoshi, Y.**, Ando, M., Araki, S., Yamaguchi, N., Tominaga, A. & Takatsu, K., (1989). Interleukin-5 induces maturation but not class switching of surface IgA-positive B cells into IgA-secreting cells. *Immunology*, 66, 32 - 38.
6. Sonoda, E., Matsumoto, R., **Hitoshi, Y.**, Ishii, T., Sugimoto, M., Araki, S., Tominaga, A., Yamaguchi, N. & Takatsu, K., (1989). Transforming growth factor  $\beta$  induces IgA production and acts additively with interleukin 5 for IgA production. *J. Exp. Med.*, 170, 1415 - 1420.
7. Mita, S., Tominaga, A., **Hitoshi, Y.**, Sakamoto, K., Honjo, T., Akagi, M., Kikuchi, Y., Yamaguchi, N. & Takatsu, K., (1989). Characterization of high-affinity receptors for interleukin 5 on interleukin 5-dependent cell lines. *Proc. Natl. Acad. Sci. USA*, 86, 2311 - 2315.
8. Enokihara, H., Furusawa, S., Nakakubo, H., Kajitani, H., Nagashima, S., Saito, K., Shishido, H., **Hitoshi, Y.**, Takatsu, K., Noma, T., Shimizu, A. & Honjo, T., (1989). T cells from eosinophilic patient produce interleukin-5 with interleukin-2 stimulation. *Blood*, 73, 1809 - 1813.
9. Takaki, S., Tominaga, A., **Hitoshi, Y.**, Mita, S., Sonoda, E., Yamaguchi, N. & Takatsu, K., (1990). Molecular cloning and expression of the murine interleukin-5 receptor. *EMBO J.*, 9, 4367-4374.
10. Murata, Y., Yamaguchi, N., **Hitoshi, Y.**, Tominaga, A. & Takatsu, K., (1990). Interleukin 5 and interleukin 3 induce serine and tyrosine phosphorylation of several cellular proteins in an interleukin 5-dependent cell line. *Biochem. Biophys. Res. Commun.*, 173, 1102-1108.
11. Mita, S., Kikuchi, Y., **Hitoshi, Y.**, Sakamoto, K., Tominaga, A. & Takatsu, K., (1990). Cyclosporin A preferentially inhibits the differentiation of murine B cells in response to IL-5 and its restoration by IL-6. *Kumamoto Med. J.*, 42, 73-86.
12. **Hitoshi, Y.**, Yamaguchi, N., Mita, S., Sonoda, E., Takaki, S., Tominaga, A. & Takatsu, K., (1990). Distribution of IL-5 receptor-positive B cells : Expression of IL-5 receptor on Ly-1(CD5)<sup>+</sup> B cells. *J. Immunol.*, 144, 4218 - 4225.

13. Enokihara, H., Kajitani, H., Nagashima, S., Tsunogake, S., Takano, N., Saitou, K., Furusawa, S., Shishido, H., **Hitoshi, Y.** & Takatsu, K., (1990). Interleukin 5 activity in sera from patients with eosinophilia. *Brit. J. Haematol.*, 75, 458 - 462.
14. Yamaguchi, Y., Suda, T., Shiozaki, H., Miura, Y., **Hitoshi, Y.**, Tominaga, A., Takatsu, K. & Kasahara, T., (1990). Role of IL-5 in IL-2-induced eosinophilia In vivo and in vitro expression of IL-5 mRNA by IL-2. *J. Immunol.*, 145, 873 - 877.
15. Yamaguchi, N., **Hitoshi, Y.**, Mita, S., Hosoya, Y., Murata, Y., Kikuchi, Y., Tominaga, A. & Takatsu, K., (1990). Characterization of the murine interleukin 5 receptor by using a monoclonal antibody. *Int. Immunol.*, 2, 181 - 187.
16. Yamaguchi, Y., Suda, T., Suda, J., Eguchi, M., Miura, Y., Mita, S., **Hitoshi, Y.**, Tominaga, A. & Takatsu, K., (1990). Analysis of eosinophil-predominant colonies formed by human hemopoietic precursor cells in the presence of purified interleukin-5. *Acta Haematol. Jpn*, 53, 688 - 698.
17. Mita, S., Takaki, S., **Hitoshi, Y.**, Rolink, A.G., Tominaga, A., Yamaguchi, N. & Takatsu, K., (1991). Molecular characterization of the beta chain of the murine interleukin 5 receptor. *Int. Immunol.*, 3, 665-672.
18. Tominaga, A., Takaki, S., Koyama, N., Katoh, S., Matsumoto, R., Migita, M., **Hitoshi, Y.**, Hosoya, Y., Yamauchi, S., Kanai, Y., Miyazaki, J.-I., Usuku, G., K-I, Y. & Takatsu, K., (1991). Transgenic mice expressing a B cell growth and differentiation factor gene (IL-5) develop eosinophilia and autoantibody production. *J. Exp. Med.*, 173, 429-437.
19. Yamaguchi, N., **Hitoshi, Y.**, Takaki, S., Murata, Y., Migita, M., Kamiya, T., Minowada, J., Tominaga, A. & Takatsu, K., (1991). Murine interleukin 5 receptor isolated by immunoaffinity chromatography: comparison of determined N-terminal sequence and deduced primary sequence from cDNA and implication of a role of the intracytoplasmic domain. *Int. Immunol.*, 3, 889-898.
20. **Hitoshi, Y.**, Yamaguchi, N., Korenaga, M., Mita, S., Tominaga, A. & Takatsu, K., (1991). In vivo administration of antibody to murine IL-5 receptor inhibits eosinophilia of IL-5 transgenic mice. *Int. Immunol.*, 3, 135-139.
21. Migita, M., Yamaguchi, N., Mita, S., Higuchi, S., **Hitoshi, Y.**, Yoshida, Y., Tomonaga, M., Matsuda, I., Tominaga, A. & Takatsu, K., (1991). Characterization of the human IL-5 receptors on eosinophils. *Cell. Immunol.*, 133, 484-497.
22. Korenaga, M., **Hitoshi, Y.**, Yamaguchi, N., Sato, Y., Takatsu, K. & Tada, I., (1991). The role of interleukin-5 in protective immunity to *Strongyloides venezuelensis* infection in mice. *Immunology*, 72, 502-507.
23. Sonoda, E., **Hitoshi, Y.**, Yamaguchi, N., Ishii, T., Tominaga, A., Araki, S. & Takatsu, K., (1992). Differential Regulation of IgA Production by TGF- $\beta$  and IL-5: TGF- $\beta$  induces Surface IgA-Positive Cells Bearing IL-5 Receptor, Whereas IL-5 Promotes Their Survival and Maturation into IgA-Secreting Cells. *Cell. Immunology*, 140, 158-172.

24. **Hitoshi, Y.**, Okada, Y., Sonoda, E., Tominaga, A., Makino, M., Suzuki, K., Kinoshita, J., Komuro, K., Mizuochi, T. & Takatsu, K., (1993). Delayed progression of a murine retrovirus-induced acquired immunodeficiency syndrome, MAIDS, in X-linked immunodeficient mice. *J. Exp. Med.*, 177, 621-626.
25. Katoh, S., Bending, M.M., Kanai, Y., Shultz, L.D., **Hitoshi, Y.**, Takatsu, K. & Tominaga, A., (1993). Maintenance of CD5+ B cells at an early developmental stage by interleukin-5 transgenic mice. *DNA AND CELL BIOLOGY*, 12, 481-491.
26. Nagai, H., Yamaguchi, S., Inagaki, N., Tsuruoka, N., **Hitoshi, Y.** & Takatsu, K., (1993). Effect of anti-IL-5 monoclonal antibody on allergic bronchial eosinophilia and airway hyperresponsiveness in mice. *Life sciences*, 53, 243-247.
27. **Hitoshi, Y.**, Sonoda, E., Kikuchi, Y., Yonehara, S., Nakauchi, H. & Takatsu, K., (1993). Interleukin 5 receptor positive B cells, but not eosinophils, are functionally and numerically influenced in the mice carrying the X-linked immune defect. *Int. Immunology*, 5, 1183-1190.
28. Fukuba, Y., Inaba, M., Taketani, S., **Hitoshi, Y.**, Adachi, Y., Tokunaga, R., Inaba, K., Takatsu, K. & Ikehara, S., (1994). Functional analysis of thymic B cells. *Immunobiol.*, 190, 150-163.
29. Miyake, K., Yamashita, Y., **Hitoshi, Y.**, Takatsu, K. & Kimoto, M., (1994). Murine B cell Proliferation and Protection from Apoptosis with an Antibody against a 105-kD Molecule: Unresponsiveness of X-linked Immunodeficient B Cells. *J. Exp. Med.*, 180, 1217-1224.
30. Sato, S., Katagiri, T., Takaki, S., Kikuchi, Y., **Hitoshi, Y.**, Yonehara, S., Tsukada, S., Kitamura, D., Watanabe, T., Witte, O. & Takatsu, K., (1994). IL-5 receptor-mediated tyrosine phosphorylation of SH2/SH3-containing proteins and activation of Bruton's tyrosine and Janus 2 kinases. *J. Exp. Med.*, 180, 2101-2111.
31. Uehara, S., **Hitoshi, Y.**, Numata, F., Makino, M., Howard, M., Mizuochi, T. & Takatsu, K., (1994). An IFN- $\gamma$ -dependent pathway plays a critical role in the pathogenesis of murine immunodeficiency syndrome induced by LP-BM5 MuLV murine leukemia virus. *Int. Immunol.*, 6, 1937-1947.
32. Korenaga, M., **Hitoshi, Y.**, Takatsu, K. & Tada, I., (1994). Regulatory effect of anti-interleukin 5 monoclonal antibody on intestinal worm burden in a primary infection with *Strongyloides Venezuelensis* in mice. *Int. J. Parasitology*, 24, 951-957.
33. Korenaga, M., **Hitoshi, Y.**, Takatsu, K. & Tada, I., (1995). Cross-resistance between *Strongyloides vebezuelensis* and *S. ratti* in mice. *J. Helminthology*, 69, 119-123.
34. Makino, M., Yoshimatsu, K., Azuma, M., Okada, Y., **Hitoshi, Y.**, Yagita, H., Takatsu, K., & Komuro, K., (1995). Rapid development of murine AIDS is dependent of signals provided by CD54 and CD11a. *J. Immunol.*, 155, 974-981.
35. Numata, F., **Hitoshi, Y.**, Uehara, S., & Takatsu, K. (1997). The *xid* mutation plays an important role in delayed development of murine acquired immunodeficiency syndrome. *Int. Immunol.*, 9, 139-46.

36. **Hitoshi, Y.**, Lorens, J. B., Kitada, S.-I., Fisher, J., LaBarge, M., Ring, H. Z., Francke, U., Reed, J. C., Kinoshita, S., & Nolan, G. P. (1998). Toso, a cell surface, specific regulator of Fas-induced apoptosis in T cells. *Immunity*, 8, 461-471
37. Rothenberg, M., Fisher, J., Zapol, D., Anderson, D., **Hitoshi, Y.**, Achacoso, P., and Nolan, G.P., (1998) Intracellular combinatorial chemistry with peptides in selection of Caspase-like inhibitors. NATO ASI Series, Vol. H 105:171-183. *Gene Therapy*.
38. Xu, X., Leo, C., Jang, Y., Chan, E., Padilla, D., Huang, B.C., Lin, T., Gururaja, T., **Hitoshi, Y.**, Lorens, J.B., Anderson, D.C., Sikic, B., Luo, Y., Payan, D.G., & Nolan, G.P. (2001). Dominant effector genetics in mammalian cells. *Nat. Genet.* 23-29
39. Kaspar, A.A., Okada, S., Kumar, J., Poulain, F.R., Drouvalakis, K.A., Kelekar, A., Hanson, D.A., Kluck, R.M., **Hitoshi, Y.**, Johnson, D.E., Froelich, C.J., Thompson, C.B., Newmeyer, D.D., Anel, A., Clayberger, C., & Krensky, A.M. (2001) A distinct pathway of cell-mediated apoptosis initiated by granulysin. *J Immunol.*, 167, 350-356.
40. Perez, O. D., Kioshita, S., **Hitoshi, Y.**, Payan D. G., Kitamura T., Nolan, G. P., & Lorens J. B., (2002). Activation of the PKB/AKT pathway by ICAM2. *Immunity*, 16, 51-65
41. **Hitoshi, Y.**, Gururaja, T., Pearsall, D. M., Lang, W., Sharma, P., Huang, B., Catalano, S. M., McLaughlin, J, Pali, E., Peelle, P., Vialard, J., Janicot, M., Wouters, W., Luyten, W., Bennett, M. K., Anderson, D. C., Payan, D. G., Lorens, J. B., Bogenberger, J., and Demo, S. (2003) Cellular localization and anti-proliferative effect of peptides discovered from a functional screen of a retrovirally-delivered random peptide library. *Chem Biol.*, 10, 975-987
42. Gururaja T, Li W, Catalano S, Bogenberger J, Zheng J, Keller B, Vialard J, Janicot M, Li L, **Hitoshi Y**, Payan DG, Anderson DC. (2003) Cellular interacting proteins of functional screen-derived antiproliferative and cytotoxic peptides discovered using shotgun peptide sequencing. *Chem Biol.*, 10, 927-937.
43. Lorens, J.B., Pearsall, D.M., Swift, S.E., Peelle, B., Armstrong, R., Demo, S.D., Ferrick, D.A., **Hitoshi, Y.**, Payan, D.G. and Anderson, D. Stable, stoichiometric delivery of diverse protein functions. (2004) *Journal of Biochemical and Biophysical Methods* 58, 101-110.

## Patent

1. Toso, a cell-surface specific regulator of Fas-induced apoptosis in T cells  
Stanford Docket S98-019